Temporal muscle thickness is an independent prognostic marker in patients with progressive glioblastoma: translational imaging analysis of the EORTC 26101 trial

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Abstract: BACKGROUND: Temporal muscle thickness (TMT) was described as surrogate marker of skeletal muscle mass. This study aimed to evaluate the prognostic relevance of TMT in patients with progressive glioblastoma. METHODS: TMT was analyzed on cranial magnetic resonance images of 596 patients with progression of glioblastoma after radio-chemotherapy enrolled in the EORTC 26101 trial. An optimal TMT cutoff for overall survival (OS) and progression free survival (PFS) was defined in the training cohort (n=260, phase 2). Patients were grouped as "below" or "above" the TMT cutoff and associations with OS and PFS were tested using the Cox model adjusted for important risk factors. Findings were validated in a test cohort (n=308, phase 3). RESULTS: An optimal baseline TMT cutoff of 7.2 mm was obtained in the training cohort for both OS and PFS (AUC=0.64). Univariate analyses estimated a hazard ratio (HR) of 0.54 (95% CI: 0.42, 0.70, p<0.0001) for OS and a HR of 0.49 (95% CI: 0.38, 0.64, p<0.0001) for PFS for the comparison of training cohort patients above versus below the TMT cutoff. Similar results were obtained in Cox models adjusted for important risk factors with relevance in the trial for OS (HR of 0.54, 95% CI: 0.41, 0.70, p<0.0001) and PFS (HR of 0.47, 95% CI: 0.36, 0.61, p<0.0001). Results were confirmed in the validation cohort. CONCLUSION: Reduced TMT is an independent negative prognostic parameter in patients with progressive glioblastoma and may help to facilitate patient management by supporting patient stratification for therapeutic interventions or clinical trials.

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Original article

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Abstract

Background: Temporal muscle thickness (TMT) was described as surrogate marker of skeletal muscle mass. This study aimed to evaluate the prognostic relevance of TMT in patients with progressive glioblastoma.

Methods: TMT was analyzed on cranial magnetic resonance images of 596 patients with progression of glioblastoma after radio-chemotherapy enrolled in the EORTC 26101 trial. An optimal TMT cutoff for overall survival (OS) and progression free survival (PFS) was defined in the training cohort (n=260, phase 2). Patients were grouped as "below" or "above" the TMT cutoff and associations with OS and PFS were tested using the Cox model adjusted for important risk factors. Findings were validated in a test cohort (n=308, phase 3).

Results: An optimal baseline TMT cutoff of 7.2 mm was obtained in the training cohort for both OS and PFS (AUC=0.64). Univariate analyses estimated a hazard ratio (HR) of 0.54 (95% CI: 0.42, 0.70, p<0.0001) for OS and a HR of 0.49 (95% CI: 0.38, 0.64, p<0.0001) for PFS for the comparison of training cohort patients above versus below the TMT cutoff. Similar results were obtained in Cox models adjusted for important risk factors with relevance in the trial for OS (HR of 0.54, 95% CI: 0.41, 0.70, p<0.0001) and PFS (HR of 0.47, 95% CI: 0.36, 0.61, p<0.0001). Results were confirmed in the validation cohort.

Conclusion: Reduced TMT is an independent negative prognostic parameter in patients with progressive glioblastoma and may help to facilitate patient management by supporting patient stratification for therapeutic interventions or clinical trials.

Keywords: recurrent glioblastoma; temporal muscle thickness; sarcopenia; overall survival; progression free survival

Keypoints:

- TMT is an independent prognostic parameter in patients with progressive glioblastoma.
- TMT is a fast and easily assessable parameter on routine MR images of the brain.
- TMT may help to objectively define frail patient populations.

Importance of the study

Besides molecular and histopathological determinants, patients' frailty is a key parameter to be taken into account for patient stratification. However, clinical frailty parameters are mainly subjective and markers to objectively define patients' frailty are urgently needed. Temporal muscle thickness (TMT) has been shown to be a suitable surrogate marker for skeletal muscle mass and therefore a potential parameter to determine sarcopenia, which is known to have an impact on the outcome of cancer patients. Here we show in a large and well-characterized cohort of patients treated in a prospective clinical trial with the use of an independent validation set that TMT is an independent and strong prognostic parameter in patients with progressive glioblastoma. TMT may serve as objectively assessable surrogate parameter of sarcopenia and patient frailty that may facilitate patient selection and stratification for therapeutic interventions or clinical trials.

Abbreviation list:

AUC	area under the curve
BMI	body mass index
CI	confidence interval
CT	computed tomography
FP	false positive
HR	hazard ratio
MGMT	O^6-methylguanine DNA methyltransferase
MRC	Medical Research Council
MRI	magnetic resonance imaging
OS	overall survival
PFS	progression-free survival
ROC	receiver operator curve
TMT	temporal muscle thickness
TP	true positive
WHO	World Health Organization

Introduction

Glioblastoma is the most frequent primary malignant brain tumor in adults and is associated with high morbidity and mortality.[1] Almost all patients experience progression within one year despite multimodal first-line therapy consisting of maximal safe surgery and combined radio-chemotherapy with the alkylating agent temozolomide.[2] Current studies evaluate the clinical benefit of various targeted agents and immunotherapies in newly diagnosed and progressive glioblastoma. Accurate patient stratification based on reliable prognostic parameters is crucial for clinical trial conduct and decision-making in clinical patient management.

Individualized therapy planning in oncology involves consideration of several parameters including molecular and histological tumor characteristics, tumor location and size as well as patient's overall physical condition. Most of these parameters are objectively assessable, however, particularly the determination of the patients' clinical condition is influenced by the subjective evaluation of the attending physician resulting in a high inter-observer variability and lack of accuracy in survival prediction.[3,4] Therefore, objectively measurable parameters to evaluate patients frailty are required to improve prognostic assessment. An emerging parameter to objectively determine patient`s physical condition is the assessment of skeletal muscle mass. A reduction of skeletal muscle mass is defined as sarcopenia, which is a key feature of cancer-related cachexia.[5]

Sarcopenia has been described as an objectively measurable parameter indicating frailty and adverse prognosis in several extracranial cancer types[6–8]. It is usually determined by measurement of the skeletal muscle cross-sectional area at the level of third lumbar vertebrae on computed tomography (CT) scans, but has not been investigated in glioblastoma so far. Whilst in most tumor patients abdominal CT scans are performed within the staging process,

these images are usually not required and consequently not available in brain tumor patients. To perform CT scans exclusively to assess information about patients' skeletal muscle mass would result in increased radiation exposure and additional healthcare costs and is therefore not feasible. However, recently published studies revealed a high correlation of lumbar skeletal muscle cross-sectional areas with temporal muscle thickness (TMT) obtained on routine diagnostic brain MR images, indicating that not exclusively lumbar muscles but also cranio-facial muscles may be a useful surrogate parameter for the estimation of skeletal muscle mass.[9,10] Swartz et al. used the cross-sectional area of skeletal muscles at the third cervical vertebra on head and neck CT images to determine sarcopenia in head and neck cancer patients.[11] Recently, TMT has been shown to be an independent prognostic parameter in patients with newly diagnosed brain metastases of melanoma, breast cancer and non-small cell lung cancer. TMT may thus serve as an objectively measurable surrogate parameter for patient frailty and survival prognosis in patients with brain tumors.[12,13]

In the current study, we investigated the prognostic role of TMT in progressive glioblastoma. To this end, we retrospectively analyzed TMT in patients enrolled in the international, prospective, randomized clinical trial European Organisation for Research and Treatment of Cancer (EORTC) 26101.

Material and Methods

Patient cohorts

We used all clinical data (including treatment group, overall and progression-free survival data, known prognostic variables for survival, and explanatory variables for TMT) that were available for all patients with first recurrence of glioblastoma who were treated in the EORTC 26101 trial (**Supplementary Table 1**). Study design and outcome of this trial have been published.[14] EORTC 26101 trial was initially designed as four-arm phase 2 trial designed to evaluate to most effective sequence of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), and the chemotherapeutic lomustine at first recurrence of glioblastoma. Close to the completion of the EORTC 26101 study, data from the BELOB phase II trial indicated an overall survival benefit of the combination of bevacizumab and lomustine over either of these agents alone.[15] As a consequence, the ongoing EORTC 26101 phase 2 trial was modified into a two-arm phase 3 trial enrolling patients in one group receiving lomustine as a single agent and one group receiving the combination of lomustine and bevacizumab. The final results of the phase 3 EORTC 26101 trial showed prolonged progression-free survival, but no overall survival advantage with combined treatment of bevacizumab and lomustine over lomustine monotherapy in progressive glioblastoma. For the current study, we used all 260 patients enrolled in the phase 2 part of the EORTC 26101 study as a training cohort and all 308 patients enrolled in the phase 3 part as a test cohort to determine the correlation of TMT measured at baseline with progression-free survival and overall survival in progressive glioblastoma (**Supplementary Table 1**). **This patient stratification design has been selected because it was considered to be more dissimilar and independent, due to the different phases of the trial separated by a gap of time with different follow-up times, than pooling datasets from phase 2 and**

phase 3 part of the EORTC 26101 study and performing a random split into training and test datasets.

Patients provided written informed consent for translational research and ethics committee approval was obtained.

TMT assessment on cranial MR images

For the present study, we retrospectively retrieved the baseline MR images obtained at enrollment into EORTC 26101 before initiation of study treatment. Baseline information on TMT was available for 568 of 596 patients (95.3%) which were used for subsequent analyses. A total of 28 of 596 patients (4.7%) were excluded from further analyses due to unavailability (n=5) or inadequacy (motion artifacts, n=8; only partial depiction of both temporal muscles, n=7; or prior therapeutic intervention with bilateral involvement of the temporal muscle, n=8) of MRI examinations (**Supplementary Figure 1**).

The measurements were performed on axial isotropic (1x1x1 mm) contrast-enhanced T1-weighted MR images without fat-saturation perpendicular to the long axis of the temporal muscle at the level of the Sylvian fissure (anterior-posterior landmark) and the orbital roof (cranio-caudal landmark).[12,13] The MRI plane was oriented parallel to the anterior commissure-posterior commissure line. TMT was measured by a board-certified radiologist (JF) who was blinded to all clinical patient characteristics including clinical outcome measures (OS and PFS). The measurements were assessed on the left and on the right side separately and were further summed up and divided by two, resulting in a mean TMT per patient. If there were any signs of previous intervention on one side that could affect the thickness of the temporal muscle (e.g., preceding craniotomy with concomitant muscle edema

or subsequent muscle atrophy), this side was excluded from the measurements and only the temporal muscle of the other side of this patient was used for further analysis. If both temporal muscles showed post-treatment changes, the patient was excluded from this retrospective study.

Statistical Analysis

Training cohort

The training cohort comprised 260 patients enrolled in the phase 2 part of the EORTC 26101 trial. Time-dependent ROC analyses were used to identify an optimal cutoff in function of OS and PFS. Predictions for an event were made at the respective median survival times. The optimal cutoff point was defined as the value that maximizes the Younden's index (i.e. value for which sensitivity + specificity - 1 is maximal). Only ROC curves with an AUC > 0.6 were considered. Hereafter, patients were grouped as "below" or "above" the TMT cutoff, which was visualized by a Kaplan Meier plot separating the TMT cutoff groups. Its association with OS and PFS was tested in a univariate Cox model. A two-sided 5% significance level was used to determine significance of the results.

This step was repeated in a multivariate model to check whether the possible effect of TMT was not confounded by important prognostic variables. The multivariate model for OS and PFS was constructed through automated stepwise backward selection of possible prognostic variables (excluding TMT) with a 5% p-value threshold. The multivariate Cox model for PFS was stratified for treatment arm.

Test cohort

The test cohort comprised 308 patients enrolled in the phase 3 part of the EORTC 26101 trial and was used to validate the findings of the analyses performed in the training cohort. Patients in the test cohort were classified as "below" or "above" the TMT cutoff obtained in the training cohort. A log-rank test was performed, visualized by a Kaplan Meier plot separating the TMT cutoff groups. The association between with OS and PFS was again tested in the uni- and multivariate Cox model. In order to be validated, the association had to be of the same magnitude as the effect in the training cohort and unidirectional. A two-sided 5% significance level was used to determine significance of the results. Sensitivity and specificity were used as a measure for discriminative ability of the model.

Training and test cohort

Continuous variables were presented by their median and quartiles. Categorical variables were presented as frequencies and percentages. A difference of 10% was considered clinically relevant.

The correlation with mean TMT and possible explanatory variables was obtained by Spearman rank correlation method for continuous variables (BMI and age) and $\sqrt{R^2}$ obtained through univariate linear models for categorical variables (gender, WHO performance status, and steroid use). A correlation coefficient of at least +/-0.3 (weak correlation) was predefined as threshold.

Univariate Cox regression analysis in function of mean TMT as a continuous covariate was used to test its association with OS and PFS. Martingale residuals were used to assess the linearity assumption.

Results

Patient and clinical characteristics

The training cohort consisted of 260 patients and the test cohort comprised 308 patients. The prevalence of baseline patient and clinical trial characteristics was similar for the training and test cohort except for treatment arm and phase (by default) and maximum diameter of the target lesion, when considering a difference of 10% as clinically relevant (see **Supplementary Table 1**). Patients in the training cohort had more often a target lesion ≥ 40 mm diameter than patients in the test cohort: 52.7% vs 42.2%. In both the training and test cohort median OS was approximately 9 months and median PFS was approximately 3 months (see **Supplementary Figure 2**). Due to staged study design, median follow-up was longer in the training cohort (approximately 30 months) than in comparison to the test cohort (approximately 12 months).

Training cohort

In the training cohort, 194 of 260 patients (75%) had measurements for left TMT and 163 of 260 patients (63%) had measurements for right TMT. For 97 of 260 patients (37%) observations for both left and right TMT were available (Pearson correlation coefficient was 0.93). Median TMT was 7.1 mm (Q1: 2.6 – Q3: 12.0) for the left side, 7.2 mm (Q1: 3.5 – Q3: 12.7) for the right side, and 7.1 mm (Q1: 2.6 – Q3: 12.4) for the mean TMT.

Figure 1 represents examples of TMT measurements on T1-weighted contrast-enhanced MR images.

There was no relation between mean TMT and any of the explanatory variables as none of the correlation coefficients passed the predefined threshold of 0.3. The correlation between mean TMT and possible explanatory variables is summarized in **Supplementary Table 2**.

A univariate Cox model for OS and PFS in function of mean TMT in mm as a continuous variable resulted in HR of 0.79 (95% CI: 0.72 – 0.86, p<0.0001) and 0.77 (95% CI: 0.71 – 0.84, p<0.0001). The association of mean TMT with outcome was approximately linear (results not shown).

The time-dependent ROC analysis for OS at 9 months and for PFS at 3 months, discriminating between patients with an event and those who remained event-free, resulted in ROC curves with AUC = 0.64 **(Supplementary Figure 3)**. The optimal cutoff point for mean TMT corresponded to 7.2 mm for both OS and for PFS, with a true positive (TP) rate of 65% and a false positive (FP) rate of 36% for OS at 9 months and a TP rate of 63% and a FP rate of 35% for PFS at 3 months.

The cutoff value was further used to divide the training cohort in two groups. Hereafter, 132 patients (50.8%) had mean TMT values below the cutoff (i.e. <7.2 mm) whereas the TMT values of 128 patients (49.2%) were above the cutoff (i.e. ≥7.2 mm).

Kaplan Meier curves for OS and PFS separating patients with mean TMT values below (red line) and above (blue line) the cutoff are visualized in **Figure 2a and Figure 2b.**

A univariate Cox model for OS in function of the TMT cutoff resulted in a HR of 0.54 (95% CI: 0.42, 0.70, p<0.0001). Similar results were obtained with the multivariate Cox model (HR of 0.54, 95% CI: 0.41, 0.70, p<0.0001). Significant prognostic variables for OS were steroid use at baseline, HR of 1.58, 95% CI: 1.19, 2.11, p = 0.002; MGMT Status, HR of 0.51, 95% CI: 0.36, 0.72, p<0.001; maximum diameter ≥ 40mm, HR of 2.49, 95% CI: 1.41, 4.41, p = 0.002; central hemisphere involvement, HR of 1.97, 95% CI: 1.37, 2.84, p<0.001 (**Supplementary Table 3**).

Figure 3a displays that the Kaplan Meier curves for OS start to converge after roughly one

year which indicates non-proportionality of TMT curves hazards. Because of the violation of the proportionality assumption (Grambsch and Therneau test; p=0.036) a sensitivity analysis was performed whereby OS was censored at 12 months. The truncated univariate Cox model for OS in function of the TMT cutoff resulted in a HR of 0.43 (95% CI: 0.31, 0.59, p<0.0001). The same result was obtained with the truncated multivariate Cox model (**Supplementary Table 4**).

A univariate Cox model for PFS in function of the TMT cutoff resulted in a HR of 0.49 (95% CI: 0.38, 0.64, p<0.0001). Similar results were obtained for the use of the TMT cutoff in a multivariate Cox model for PFS which was stratified for treatment arm (HR of 0.47, 95% CI: 0.36, 0.61, p<0.0001). Important prognostic variables for PFS were neurological deficit, HR of 1.44, 95% CI:1.09, 1,92, p = 0.011; steroid use at baseline, HR of 1.42, 95% CI: 1.08, 1.86, p = 0.011; MGMT status, HR of 0.61, 95% CI: 0.43, 0.87, p = 0.007; number of target lesion >1, HR of 2.47, 95% CI: 1.38, 4,41, p = 0.002 (**Supplementary Table 5**).

Test cohort

Next we tried to confirm the findings of the training cohort in the test cohort. Of 308 patients of the test cohort, 217 patients (70.5%) had mean TMT values below the TMT cutoff (i.e. <7.2 mm) and 91 patients (29.5%) had mean TMT values above the cutoff (i.e. ≥7.2 mm). Kaplan Meier curves for OS and PFS separating patients in the test cohort with mean TMT values below and above the cutoff of 7.2 mm are shown in **Figure 3a** and **3b** (log-rank test p<0.0001), both for OS and PFS).

A univariate Cox model for OS in function of the TMT cutoff resulted in a HR of 0.44 (95% CI: 0.32, 0.61, p<0.0001). Similar results for the TMT cutoff were obtained with the multivariate Cox model (HR of 0.43, 95% CI: 0.31, 0.60, p<0.0001; **Supplementary Table 6**). There was no indication of a violation of the proportionality assumption according to the

Grambsch and Therneau test (p=0.18), therefore no additional sensitivity analyses were performed. The TMT cutoff of 7.2 mm resulted in a TP rate of 82% and a FP rate of 58% for OS at 9 months **(Supplementary Figure 4a)**. A univariate Cox model for PFS in function of the TMT cutoff resulted in a HR of 0.46 (95% CI: 0.35, 0.61, p<0.0001). Similar results were obtained in the multivariate Cox model stratified for treatment arm (HR = 0.50, 95% CI: 0.37, 0.66, p<0.0001, **Supplementary Table 7**). The mean TMT cutoff of 7.2 mm resulted in a TP rate of 82% and a FP rate of 59% for PFS at 3 months **(Supplementary Figure 4b)**.

Discussion

This study investigated the prognostic value of TMT in patients with glioblastoma at first progression after standard combined radiochemotherapy. We show a strong and independent prognostic role of TMT for PFS and OS. In Cox models, the risk of death and progression or death was increased by 85% and 113% in patients with a TMT below the cut-off compared to patients with a TMT above the cut-off in the training cohort (Figure 2, Supplementary Table 3 and 5). The findings of the training cohort were validated in the test cohort. Herein, the risk of death and progression or death was increased by 127% and 100%, (Figure 3, Supplementary Table 6 and 7) when comparing patients below and above the optimal TMT cutoff. These data confirm and extend findings in brain metastases patients. TMT showed a strong association with OS at the diagnosis of brain metastases. In melanoma, non-small cell lung cancer and breast cancer patients the risk of death was increased by 39%, 32% and 24%, respectively, when comparing patients below and above the TMT cutoff, which was 5.8 mm in melanoma patients, 5.9 mm in non-small cell lung cancer patients and 5.4 mm in breast cancer patients.[12,13]

Our findings were independent of prognostic parameters for OS and PFS. Furthermore, the results of the current study revealed that TMT values provide information not captured by other possible explanatory variables. First, we found no significant correlation between WHO performance score and TMT. This might reflect the high observer variability regarding the patient's physical condition which is mainly based on the subjective evaluation of the attending physician in contrast to TMT, which is an objectively assessable parameter estimating patient`s skeletal muscle mass. [8,16] Furthermore, the missing association between TMT and age indicates that skeletal muscle mass loss may yield more information about the patient`s physical condition than the chronological age alone. The findings of this study go in line with previously published data of brain metastases patients from lung and breast cancer,

where TMT only showed a low negative correlation with patient´s age.[18] Moreover, it is widely hypothesized that biological age, including patient´s frailty, is more highly associated with death than chronological age.[27,28] Thus, based on the strong independent prognostic effect of TMT the parameter could be used as stratification factor in prospective clinical trials assessing the intensity of treatment intervention tailored to patient frailty.

The results of this study suggest that TMT represents an objectively assessable parameter that may aid to improve the estimation of the prognosis of patients with recurrent glioblastoma. Despite the effect of Bevacizumab on PFS, there was no indication that baseline TMT is a predictive factor for PFS in relation to the treatment with either Bevacizumab alone versus Lomustine alone or the combination of Bevacizumab and Lomustine versus Lomustine alone both followed by the best investigators choice, as in both analyses the cutoff by treatment interaction term was not significant (results not shown).

Amongst other cranio-facial muscles the thickness of the temporal muscle was selected in this study as prognostic parameter for several reasons. The temporal muscle is one of very few muscles that can be delineated in its full extent on routinely performed cranial MR images, which is of high importance particularly in patients which have undergone craniotomy or radiation therapy and may suffer from muscular edema or atrophy. Moreover, TMT has been shown in previous studies to correlate with skeletal muscle mass and may therefore be used to asses sarcopenia in patients with primary brain tumors, in whom usually only cranial MRI and no abdominal CT images are available.[9,10,16] Furthermore, TMT has been shown to play a potential role in the prognosis of ventilator and hospital days in trauma patients and OS in newly diagnosed brain metastases patients.[12,13,19] There is also a study that used temporal muscle volume to predict the length of the hospital stay in children with non-syndromic craniosynostosis.[19,20] However, plane or volume segmentation is much more time-consuming also in case of automatic tissue segmentation, which usually relies on additional manual

corrections because it is still mostly prone to segmentation errors. In contrast, TMT measurements took only about 30 seconds per patient and its assessment is therefore an appropriate method for skeletal muscle mass estimation to be integrated in the routine clinical setting with a high inter-rater (left TMT 0.959; right TMT 0.975) and intra-rater agreement (left TMT 0.917; right TMT 0.94).[10] The key benefit that the temporal muscle can be delimited in its whole extent on routinely assessed brain MR images comes along with the consequence to deal with a relatively small muscle diameter when it comes to TMT measurement. Therefore, it is all the more important to accurately adhere to the predefined landmarks and use only isotropic 1 x 1 x 1 mm MR images to provide a high measurement accuracy and minimize partial volume artifacts.[10,12] To overcome the potential influence of oral or dental diseases on TMT, the measurements were taken on both sides and a mean TMT value was calculated in all patients. This did not show any signs of interventions (e.g. craniotomy) including the temporal muscle.[21]

Although we were able to investigate and validate TMT in two cohorts of patients enrolled in a large international, prospective, randomized clinical trial, our study faces some limitations. The retrospective analysis of TMT prohibited evaluation of anatomical-functional relationships. Although recently published data revealed that TMT is an applicable parameter to estimate skeletal muscle mass, further studies are required to assess its correlation with clinical frailty parameters such as muscle strength in a prospective setting.[10] Due to the fact, that we unexceptionally included progressive glioblastoma the measurement of bilateral temporal muscle thickness was only possible in 38% of the patients in this study cohort because of the frequent post-treatment changes including the temporal muscle at least at one side. Furthermore, in the current study we were able to investigate patients with progressive glioblastoma only. Thus, the validation of the defined cut-off value as well as the prognostic role of TMT in newly diagnosed glioblastoma or other diseases remains to be determined. We

are currently working on the validation of the TMT cut-off in an external dataset consisting of newly diagnosed glioblastoma and will report these findings separately. We will use the cut-off of 7.2 mm as a primary assumption but the identification of more optimal cut-off values per setting and disease will also be considered. Also owing to its retrospective nature, imbalances in important unmeasured prognostic factors or determinants of TMT could not be corrected for in the adjusted analyses. Moreover, although it is reported that ethnicity has an impact on skeletal muscle mass information about the ethnicity of the patients was not available in the current study. Therefore ethnic differences among the patients within the study cohort could not have been considered. Although the prognostic effect of TMT was independent from steroid use at baseline, the exact influence of duration and dose of steroid use on TMT remains to be determined in further studies, as these data were not available in our study population.

The pathobiology of TMT variation among patients with recurrent glioblastoma remains unclear at the moment. TMT may reflect general physical fitness, or could also be associated with glioblastoma-related catabolic, paraneoplastic and inflammatory processes in combination with insufficient nutrition.[22-24] In any case, the knowledge of the association between survival and skeletal muscle mass may result in additional therapeutic opportunities such as exercise training, nutritional supplements, or pharmacotherapy with myostatin inhibitors.[25-28]

In conclusion, TMT is an independent prognostic parameter in patients with recurrent glioblastoma. Assessment of TMT may aid to optimize treatment decisions as well as patient stratification for clinical trials based on an objective determination of frail patient population.

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Captions for all illustrations

Figure 1: TMT assessment represented on cranial T1-weighted contrast-enhanced MR images. **A**, a 65-year-old female patient with an overall survival of 20.6 months (median TMT = 12.4 mm), and **B**, a 35-year-old male patient with an overall survival of 9.3 months (median TMT = 3.5 mm).

Figure 2: Kaplan-Meier curve analysis according to mean TMT cutoff for OS (**a**) and PFS (**b**) in the training cohort.

Figure 3: Kaplan-Meier curve analysis according to mean TMT cutoff for OS (**a**) and PFS (**b**) in the test cohort.


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